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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/684,458	Applicant(s) GERRITSEN ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-112* is/are pending in the application.

4a) Of the above claim(s) *1-23,36-59,64-65 and 68-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-35,60-63,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,8,11*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

The Election filed March 18, 2002 (Paper No. 13) in response to the Office Action of December 18, 2001 is acknowledged and has been entered. Claims 1-112 are pending in the application and Claims 1-23, 36-59, 64-65, and 68-112 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 24-35, 60-63, and 66-67 are currently under prosecution

Applicant's election with traverse of Group 2, claims 24-35, 60-63, and 66-67 in Paper No 13 is acknowledged. It is further acknowledged that applicants have elected the PRO-C-MG.2 polypeptide corresponding to SEQ ID NO:2. The traversal is on the ground(s) that the Office has not provided an explanation or an example to support the requirement for restriction and that the Office has simply stated a conclusion of material distinctness, without support. Thus, Applicant's submit that the Office has not met the necessary burden in order to sustain the restriction requirement. This is not found persuasive. The reasons and or explanations for the restriction were set forth in Paper No. 10, pages 31-33. Furthermore, the inventions are classified differently, necessitating different searches in the literature. Classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. Furthermore, the guidelines for restriction purposes do not require both examples and reasons, only that the Examiner provide one or the other to support the conclusions (MPEP

803). For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the provisional application(s) and filing date on which priority is claimed under 35 USC 119(e).

Specification

The disclosure is objected to because of the following informalities: Pages 19-35 contain a computer program listing. The patent rules governing computer program listings in the specification can be found under 37 CFR 1.96. In particular, any listing having more than 60 lines of code that is submitted as part of the specification must be positioned at the end of the description but before the claims. Any amendment must be made by way of submission of a substitute sheet. Appropriate correction is required.

The specification is further objected to because it contains an embedded hyperlink and/or other form of browser-executable code (i.e. see page 37, line 8; page 39, line 25). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

Claim Objections

Claims 24-35, 60-63, and 66-67 are objected to in so far as they are drawn to non-elected subject matter. The objection can be obviated by amending the claims so that that they are limited to the elected PRO-C-MG.2 polypeptide (SEQ ID NO:2). Also included in the objection is reference to antagonists, agonists, and antibodies in Claims 60-61,67 and "or antibody" in Claim 63.

Claim 66 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 62. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper to object to the claims as being substantial duplicates. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-27, 32-35, 60-63, and 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-27 are rejected as vague for reciting "(DNA-C-MG.2-1176 and DNA-C-MG.12-1776, respectively)" as it cannot be determined which of these cDNA's (or if they are cDNAs) encodes the PRO-C-MG.2 polypeptide and corresponds to the cDNA deposited as PTA-798 or PTA-799. For example, it is understood that PTA-798 corresponds to a deposited

cDNA. But does this cDNA specifically encode PRO-C-MG.2? What is the significance of claiming DNA-C-MG.2-1176 and DNA-C-MG.12-1776? Clarification is requested. Amendments must be supported by the specification.

Claims 32-35, 60-63, 66-67 are rejected as vague and indefinite for reciting the term "PRO-C-MG.2" as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify PRO-C-MG.2, for example, by SEQ ID NO.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 24-35, 60-63, 66-67 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The proposed utility for the PRO-C-MG.2 protein (SEQ ID NO:2), therapeutic compositions and methods of making thereof, include methods for promoting or inhibiting angiogenesis and or vascularization, preferably neo- or cardio- vascularization in mammals, and for identifying additional molecules providing that benefit (page 3, lines 15-17). Additional purported utilities include the diagnosis, treatment, or prevention of disorder such as the

promotion or inhibition of angiogenesis, inhibition or stimulation of vascular endothelial cell growth, stimulation of growth or proliferation of vascular endothelial cells, inhibition of tumor growth , inhibition of angiogenesis-dependent tissue growth, stimulation of angiogenesis-dependent tissue growth. Also proposed are methods for treating a tumor, reducing the size of a tumor, reducing the vasculature supporting a tumor or reducing the tumor burden of a mammal by administering an effective amount of a compound of the invention (page 3, lines 17+).

However, neither the specification nor any art of record teaches what PRO-C-MG.2 is, what it does, nor to they do not teach any association with any specific disease. The asserted utility of PRO-C-MG.2 appears to be based on the isolation of cDNA clones from HUVEC's grown in various conditions (page 125, lines 15-17) wherein it was ascertained that the PRO-C-MG.2 gene "had a greater than 4-fold increase in gene expression as determined by the GeneCalling approach (page 128, lines 27-28). However, such an increase in expression says nothing about the purported biological properties of the PRO-C-MG.2 polypeptide. For example, these results do not say whether or not the PRO-C-MG.2 promotes angiogenesis or prevents angiogenesis. Many genes are overexpressed in many different tissues types, and it remains to be determined whether such overexpression translates into a polypeptide comprising the proposed utilities of the claimed invention. Moreover, there is no evidence to suggest that the claimed polypeptides are actually expressed by the tissues. Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict similar levels of translation of such mRNA into a polypeptide or predict that such a polypeptide will actually be produced. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked

during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Also, with regards to tumor associated antigens, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, the predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Furthermore, the remaining examples in the specification are prophetic and appear to require further experimentation. For example, the specification teaches (page 144, lines 8+) the in vivo anti-angiogenic effects of a PRO-C-MG.2 polypeptide antagonist are "shown" using Hydron pellets, and that these in vivo data (line 15) are consistent with the in vitro results. However, no such data has been presented to verify such activity. The specification further explores the presence of "very important domains" associated with full-length PRO-C-MG.2 (SEQ ID NO:2) (page 128, lines 20-27). However, it remains to be determined how these domains are important or relevant to the ascribed utility of the claimed polypeptide. Thus, the asserted utilities for PRO-C-MG.2, such as the generation of antibodies useful as diagnostic agents and or therapeutic agents and or methods in the treatment of some forms of cancer, wherein no specific cancer is identified, applies to many unrelated polypeptide structure sequences. Therefore, the asserted utilities are not considered "specific" utilities, i.e. they are not specific to PRO-C-MG.2.

Further, even if the polypeptide of SEQ ID NO:2 is an angiogenic-like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, or teach a relationship to any specific disease. As such, the claimed invention does not provide a "substantial" utility or real world use. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific, substantial, and well-established utility for the reasons set forth, credibility cannot be assessed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-35, 60-63, 66-67 are further rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 24, 26, and 28-31 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and therefore the written description is not commensurate in scope with the claims drawn to polypeptides with "80% sequence identity" or those "scoring at least 80% positives", or "fragments sufficient to provide a binding site" or polypeptides produced by hybridizing test DNA molecules under stringent conditions and culturing a host cell comprising the test DNA molecule under conditions suitable for the expression of the polypeptide; all of which read on naturally occurring variants of SEQ ID NO. 2.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptide fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V.*

Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Further, since the disclosure fails to describe the common attributes or characteristics that identify members of a genus, and because the genus is highly variant, the claiming of nonspecific amino acid sequences (fragments, portions, etc.) is insufficient to describe the genus and full-length genes. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only an isolated polypeptide comprising the amino acids of SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
June 12, 2002